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Title:
Modeling the Bidirectional Coupling of Localized Calcium Elevations and Whole Cell Calcium Responses

Abstract:
Localized Ca elevations known as Ca puffs and sparks are cellular signals that arise from the cooperative activity of clusters of inositol 1,4,5-trisphosphate receptors and ryanodine receptors clustered at Ca release sites on the surface of the endoplasmic reticulum or sarcoplasmic reticulum. When Markov chain models of intracellular Ca regulated Ca channels are coupled via a mathematical representation of a Ca microdomain, simulated Ca release sites may exhibit the phenomenon of stochastic Ca excitability where the IP3Rs or RyRs open and close in a concerted fashion. Such mathematical models provide insight into the relationship between single-channel kinetics and the statistics of puff/spark duration, and clarify the role of stochastic attrition, Ca inactivation, luminal depletion, and allosteric interactions in the dynamics of puff/spark termination. The stochastic dynamics of local Ca is an important aspect of excitation-contraction coupling in cardiac myocytes, where sarcoplasmic reticulum Ca-induced Ca release is locally controlled by trigger Ca influx via L-type channels of the plasma membrane. A recently developed whole cell modeling approach is able to avoid the computationally demanding task of resolving spatial aspects of global Ca signaling by using probability densities and associated moment equations to representing heterogeneous local Ca signals in a population of Ca release units. This new class of whole cell models of Ca handling facilitates simulation and analysis of the bidirectional coupling of localized calcium elevations and whole cell calcium responses in cardiac myocytes.